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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,515	03/19/2004	Masayoshi Yamaguchi	671302-2006	7637
20999	7590	11/03/2005	EXAMINER	
FROMMER LAWRENCE & HAUG 745 FIFTH AVENUE- 10TH FL. NEW YORK, NY 10151			LIETO, LOUIS D	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/804,515	Applicant(s) YAMAGUCHI, MASAYOSHI	
	Examiner Louis D. Lieto	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 1-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/19/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response to the restriction requirement was received on 9/29/2005. Claims 1-40 are pending in the instant application. Applicants elected the subject matter of Group III, claims 25-40, drawn to a drawn to an animal model having bone pathology, wherein the animal model over expresses regucalcin and shows bone pathology, a screening method of preventive and therapeutic agents, and a therapeutic agent. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 9/29/2005.

Claims 25-40 are under consideration.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, it is noted that applicant has not provided an English translation of the foreign priority papers.

Information Disclosure Statement

The references cited in the information Disclosure Statement filed on 3/19/04 have only been considered on the basis of the supplied English abstracts.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of multiple uses of the legal phrase "said". For example see lines 6,7 and 11 of the Abstract. Correction is required. See MPEP § 608.01(b).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 40 is rejected under the judicially created doctrine of double patenting over claims 1-18 of U. S. Patent No. 6,806,252 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: The instant claim 40 is drawn to a preventive or therapeutic agent for bone disease. This is a product by process claim. The patentability of a product-by-process claim is determined without consideration of the process for making it, which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Claim 40 is drawn to a broad genus of preventive or therapeutic agents for bone disease. Claims 1-18 of U. S. Patent No. 6,806,252 recite species of bone-strengthening agents. Said agents are members of the claimed genus of the instant claim 40. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application, which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Objections

Claims 33 and 34 objected to because of the following informalities: They are drawn to female non-animals. This phrase has no literal meaning, since by definition only animals have sexes. Appropriate correction is required.

Claim 39 is objected to because of the following informalities: The claim is drawn to a method of treating aosteoporosis. This is an obvious misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass any non-human animal that overexpressed regucalcin and shows bone pathology. However, there is no requirement that said animal is transgenic or otherwise shows intervention by the hand of man. Therefore a wild-type animal of any species that over expressed regucalcin and showed age-onset osteoporosis would satisfy the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat comprising a transgene comprising the rat regucalcin cDNA, wherein the rat overexpresses regucalcin, which causes a decrease in bone density, bone strength or bone thickness, a method of using said transgenic rat in a screening method for

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preventative and therapeutic agents, and a therapeutic or preventative agent, does not reasonably provide enablement for any non-human animal that overexpresses regucalcin and shows bone pathology, a method of using said animal in a screening method for preventative and therapeutic agents, and a therapeutic or preventative agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims encompass any non-human animal that overexpresses regucalcin and shows bone pathology, including any native and transgenic animals, such as geese, monkeys, donkeys, snails, salamanders, frogs, bumble bees and salmon. Wherein the changes in bone morphology are detected by measuring any changes in vulnerability of bone tissue, change of bone morphology, delay in bone growth, Further, the claims encompass using any of these animals in a screening method for preventative and therapeutic agents, and a therapeutic or preventative agent.

The specification also fails to provide adequate guidance and evidence for the production of any transgenic animals over-expressing any regucalcin, which causes bone pathology other than the transgenic regucalcin rat with bone loss. Further, the art of transgenics at the time of filing held that the phenotype of transgenic animals was unpredictable. Kolb et al., who states that “the expression of foreign genes in transgenic animals is generally unpredictable as transgenes integrated at random after pro-nuclear injection into fertilized oocytes” because of inhibition by neighboring chromatin {Kolb et al. (1999) Gene 227:21-31; Abstract}. The phenotype produced by a specific transgene was not predictable in different species at the time of filing. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that

variation in the genetic background contributes to the unpredictability of the resulting phenotypes of transgenic or gene-targeted animals. “Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype” (e.g. abstract). Sigmund further states that “many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These “epigenetic” effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments” (e.g. introduction).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that “animal transgenics is still suffering from technical limitations” (e.g. abstract). “Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and “For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells” (e.g. p. 148, right column).

Even in respect to rodents, the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the art of transgenics is such that one of skill in the art would be able to produce a transgenic rat comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of

a transgene as well as the resulting phenotype of the transgenic rat are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. These issues become even more complicated when working with more than one transgene, especially when the products of one transgene regulate the expression of the other. The complex problems associated with transgenesis are illustrated by Houdebine et al., who states that “numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted” {Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2: The expression of transgenes}. Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other animals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col. 1, pgph 3). As Murray states, “the observation that the oMT1a-oGH transgene that is regulated in mice is uncontrollable in both sheep and pigs suggests that transgene constructs still need to be tested in the species of interest.” {Murray (1999) Theriogenology 51:149-159; pg. 150, pgph 4}. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification of the production of any transgenic regucalcin animals other than a transgenic regucalcin rat, it would have required undue

experimentation to predict the results achieved in any of the other animals and their corresponding phenotypes as embraced by the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-29, 31-34, 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26, 32, 34 are drawn to an animal model “wherein the animal expresses one or more bone pathology of any vulnerability of bone tissue, change of bone morphology or delay in bone growth.” An animal cannot express bone pathology, they can only show pathological changes in bone morphology. Further, the specification does not make clear what the differences are between any vulnerability of bone tissue and changes in bone morphology. Finally, the claims encompass any increase or decreases in “any vulnerability of bone tissue, change of bone morphology or delay in bone growth.” However, it is unclear how a decrease in “any vulnerability of bone tissue” is pathological. Therefore the metes and bounds cannot be determined. Claims 32 and 34 depend from claim 26.

Claims 31 and 33 are drawn to a “non-human animal that overexpresses regucalcin is a transgenic non-human animal to which regucalcin gene is introduced.” It is unclear from the specification if these claims are intended to encompass a transgenic regucalcin animal or an animal transgenic for any other gene that is subsequently transfected with a regucalcin gene. Therefore the metes and bounds cannot be determined. Claim 33 depends from claim 31.

Claims 27-29 and 36-38 are drawn to a "measurement estimation." It is unclear from the specification if these claims are intended to indicate that measurements of bone morphology or biochemistry are to be taken, or if they are merely to be estimated. Further, if measurements are to estimated what is included in such an estimation, it could include measuring the thickness of a femur by a rough eyeball view of the bone or it could include measuring the bone thickness with an x-ray and rounding the thickness to the nearest angstrom. Therefore the metes and bounds cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-35 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamaguchi et al. {Yamaguchi et al. (Published on-line June 24, 2002) J. Cell. Biochem 86:520-529}.

It is noted that the reference of Yamaguchi et al. shares co-authorship with the inventor of the instant application. However, the reference of Yamaguchi et al. was also written by Y. Morooka, H. Misawa, Y. Tsurusaki, and R. Nakajima, who are not listed as inventors of the instant invention. Therefore the reference of Yamaguchi et al. was written by a different inventive entity than the that of the instant invention. Further, Applicant cannot rely upon the

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foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Yamaguchi et al. provides guidance on a method of making transgenic rats that overexpress regucalcin (Abstract). Wherein a DNA fragment containing the regucalcin gene in pCXN2 was used for pronuclear microinjection of SD rat embryos to generate transgenic rats. The founder rats were mated to produce F1 litters. Male and female heterozygote rats were identified and bred to homozygosity (pg. 521, Materials and Methods, Col. 2). These transgenic regucalcin rats inherently have increased bone loss as taught by Yamaguchi² et al. {Yamaguchi² et al. (2002) Int. J. Mol. Med. 10:377-383}. Further, “When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent.” See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant’s product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Therefore, by teaching all the limitations of the claims as written, Yamaguchi et al. clearly anticipates the instant invention as claimed.

Claim 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Downs et al. {Downs et al. (1999) Calcif. Tissue Int 64 :463-469}.

Downs et al. teaches the treatment of osteoporosis in elderly human women with Alendronate (ALN) (Abstract). ALN therapy increased or maintained bone mass density of the spine, trochanter and forearm (Abstract). Applicant's claims are drawn to a product, such as a preventative or therapeutic agent for bone disease. This would include a drug used to treat osteoporosis. However, "when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Therefore, by teaching all the limitations of the claims as written, Downs et al. clearly anticipates the instant invention as claimed.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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